Title: Is Breast Always Best? Breastfeeding and Lithium

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Breastfeeding confers clear public health benefits to mother and infant[1]. Over the past 20 years, the fertility of women with severe mental disorders including bipolar disorder and schizophrenia has increased[2,3] This warrants attention to the clinical question of how to weigh the benefits versus risks of breastfeeding in this population.

The early postpartum period is a time of significant risk of relapse for women with severe mental disorders[2]. Such relapse is associated with considerable distress for women, and can result in separation from their infant for hospital admission and the potential removal of the infant from maternal care. To reduce the risk of relapse, a comprehensive relapse prevention plan that includes prophylactic medication, minimising sleep deprivation, reduction in stimulation and psychosocial support is encouraged and such a plan might be incompatible with breastfeeding [4,5].

Lithium carbonate is an effective and preferred treatment for acute mania and longer term for relapse prevention for both mania and depression[4,6]. There is also growing evidence of its efficacy for prevention and treatment of postpartum psychosis [4]. Lithium is a renally excreted agent with a narrow therapeutic range (0.6-0.8 mmol/l). Levels associated with serious toxicity are only slightly higher than the therapeutic range[6] Lithium is also associated with a range of neurological, cardiovascular, renal and endocrine side effects with some side effects such as, tremor and thyroid abnormalities occurring within the therapeutic range. As lithium does pass into the breast milk, many experts, and international guidelines, agree that the risks of infant lithium exposure outweigh the benefits of breastfeeding[7]. However, in our collective experience across 4 continents women (and prescribers) are increasingly expressing a desire to breastfeed on lithium. As such, a careful consideration of the risks and benefits of breastfeeding in the setting of maternal lithium treatment is required.

The key factors are the amount of exposure and the implications any exposure may have for infant health outcomes. Most authorities regard a relative infant dose of less than 10% as safe in terms of exposure levels, although this does not fully reassure if there is any potential for small exposures for a particular agent to cause harm. Infant lithium levels range from 30-40% of maternal levels, with relative infant dose ranges of 12-30%,[5,8] although findings vary greatly between studies[9]. In the short-term, this may present some risks. An infant's capacity to clear agents through renal excretion is more limited than an adult. Fluid balance in infants can be easily influenced by climate,

infection, exclusive breastfeeding and other factors, making dehydration more likely in young babies. In turn, this increases the risk that infant serum lithium may reach toxic levels.

Only 36 cases of lithium exposure in breastfeeding have been reported in the scientific literature so knowledge of the range of risks and even levels of exposure is poor[9,10]. Within these reports there is a both a case report of hypotonia (that resolved)[11] and a case series of 10 infants which reported that 4 of 10 infants had either an abnormality on thyroid stimulating hormone (TSH) (a major concern as the long term consequences of hypothyroidism on cognitive and neurodevelopment are well recognised) or changes in blood urea nitrogen (BUN) or creatinine indices[12]. The risk of effects on thyroid, renal and lithium toxicity can be monitored through regular blood tests but paediatric phlebotomy can be traumatic for parents and infants. Furthermore, the infant identified with high TSH and the infant with high BUN had infant lithium serum levels of 0.23[12] and 0.10[12] respectively, indicating abnormalities despite low lithium levels. While there are short term reports on outcomes for these infants, the longer-term significance of exposure or associated abnormalities is unclear [9,10].

In low and middle-income countries (LAMI) decision-making may be even more complicated. The combination of prohibitive costs of formula feeds, high rates of infant morbidity and mortality due to infections (especially diarrhoeal diseases), inadequate hygiene practices related to bottle feeds, lack of community based psychiatry teams for follow up, and long distances from health care may put infants at risk if breastfeeding is discouraged. However, frequent monitoring of lithium levels and renal function in the infant would be impossible and the likelihood of risk of lithium toxicity to the infant in case of dehydration and diarrhoea very high. Therefore, on balance if a woman has to be on lithium, in low resource situations, breastfeeding may not be a viable option.

For preterm babies, the concerns about not offering breast milk also include neonatal necrotising enterocolitis, with the risk 20 times higher in formula fed babies than those fed with breastmilk[1]. However, this needs to be balanced with exposure to an agent with unknown longer-term effects in a neonate far more vulnerable to environmental exposure than a neonate born at term. Breast milk banks, if available, could be a clinical option.

Women who require lithium treatment in the postpartum do so because of the severity of their illness. Ideally any change in maintenance medication because of a

desire to breastfeed would be tried pre-conception, rather than during the perinatal period at a time of increased vulnerability. As part of any care in the perinatal period, clinicians and women carefully consider options around treatments, and individual choices should be supported. For many women, remaining on an effective and proven treatment gives them the best chance for developing a strong and healthy mother-infant relationship with confidence and capacity as a parent.

While the best start to life includes good quality nutrition, such as breast milk, of equal or potentially greater benefit is a healthy relationship with a mentally well primary caregiver. We believe that it is important to focus on ways to support women who require lithium to feel confident and positive about parenting their baby, and experience the closeness of the mother-infant bond without needing to breastfeed. At this point in our understanding of lithium and breastfeeding, there appears to be the potential to do harm. With our understanding of the importance of early development for determining lifelong health and wellbeing, is this risk worth taking?

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